(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 April 2004 (29.04.2004)

PCT

(10) International Publication Number
WO 2004/035565 A1

(51) International Patent Classification[7]: C07D 401/12

(21) International Application Number:
PCT/SE2003/001602

(22) International Filing Date: 15 October 2003 (15.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0203092-2 18 October 2002 (18.10.2002) SE

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG; US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

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WO 2004/035565 A1

(54) Title: METHOD FOR THE SYNTHESIS OF A BENZIMIDAZOLE COMPOUND

(57) Abstract: A process for the manufacture of omeprazole or esomeprazole from pyrmethyl alcohol via pyrmethyl chloride and pyrmetazole characterized in that the whole reaction sequence is carried out without any isolation or purification of intermediates. Further, the reaction is carried out in a solvent system common for the whole reaction sequence and inert to the reactants formed during the process and used in the process and comprises a water immiscible organic solvent and a specified amount of water.

METHOD FOR THE SYNTHESIS OF A BENZIMIDAZOLE COMPOUND

The present invention relates to an improved process for the synthesis of 5-methoxy-2(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)thio)-1H-benzimidazole (pyrmetazole) used in the manufacturing of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole and its (*S*)-enantiomer, known under the generic names omeprazole and esomeprazole, respectively.

Background of the invention and prior art

An efficient process for synthesis of omeprazole is described in WO 97/22603, which is hereby incorporated by reference. In the described process, there is no need for additional purification or isolation steps in between the different reaction steps and a more efficient process is hence offered. Further adding to the simplicity, the reaction sequence is carried out in one common solvent system throughout the whole process. However, there is still a need of a new, even more convenient and more efficient process for the manufacturing of pyrmetazole in higher yield and with higher purity, and which process provides increased yield of the final products, omeprazole or esomeprazole.

Summary of the invention

The object of the invention is to provide a process for the manufacturing of pyrmetazole in a high yield and with a high purity, which is especially important for the asymmetric synthesis of esomeprazole. The process, i.e. the reaction sequence from pyrmethyl alcohol (Ia) to pyrmetazole (I), is carried out, without any isolation or purification of intermediates, in one solvent system common for the reaction sequence, to obtain a reproducible high yield of the final products, omeprazole or esomeprazole. Such a process eliminates time consuming steps for isolation or purification of intermediates and save time on avoiding solvent changes in the process, thus making the process more efficient and with a high production capacity.

Detailed description of the invention

The process comprising the following reaction steps:

Step 1: Pyrmethyl alcohol (Ia) + chloro-dehydroxylating agent ⟶ pyrmethyl chloride (Ib)

Step 2: Pyrmethyl chloride (Ib) + metmercazole (Ic) ⟶ pyrmetazole (I)

is performed in a solvent system common for the reaction sequence, comprising a water immiscible organic solvent and a specified amount of water added. This process is used for the synthesis of pyrmetazole, an intermediate in the synthesis of omeprazole or esomeprazole.

In Step 1, the conversion of pyrmethyl alcohol into pyrmethyl chloride, hereinafter referred to as chloro-dehydroxylation, the pyrmethyl alcohol (Ia) is reacted with an excess of a chloro-dehydroxylating agent giving an alkyl chloride, i.e. pyrmethyl chloride (Ib). The chloro-hydroxylating agent can be selected from thionyl chloride, cyanuric chloride, phosphorous trichloride, phosphorous pentachloride, and phosphorous oxychloride. The reaction is performed at a temperature of -5° C to +45 ° C, preferably between -5° C and +35° C, most preferably between +10° C and +35° C, or between +25° C and +35° C. In the case, where no water is present from the beginning, the conversion of the reactants into the product, pyrmethyl chloride (Ib), will not go to completion. However, the reaction can be re-started by adding a specified amount of water and the reaction thereafter can be completed. Thus, if the reaction ceases, it is possible to re-start it with addition of a specified amount of water.

According to Step 2 above, pyrmethyl chloride (Ib), provided from Step 1, is reacted with metmercazole (Ic) under alkaline conditions, e.g. an alkaline aqueous solution of metmercazole (Ic) is prepared and mixed with the pyrmethyl chloride (Ib). The reaction is preferably carried out at a temperatue of +30° C to +60° C during a prolonged period of time. Metmercazole (Ic) is charged in approximately stoichiometric amount to the pyrmethyl chloride (Ib). The invention may also be used in combination with a phase

transfer catalyst, for instance a quarternary amine, such as tetrabutyl ammonium bromide. The two phases formed are separated, the aqueous phase may be extracted with a water immiscible organic solvent such as toluene, and the organic phase may be extracted with water.

As pyrmethyl alcohol (Ia) has a disadvantageous effect on the following reaction steps, it is important to minimise the content of the pyrmethyl alcohol (Ia) present.

The reaction sequence according to Step 1 and Step 2 described above is carried out in one solvent system. The solvent system used for the present reaction sequence comprises a water immiscible organic solvent, such as halogenated, aliphatic or aromatic hydrocarbons or esters, for example toluene, ethyl acetate and methylene chloride, and a specified amount of water added. Preferably, toluene may be used as the water immiscible organic solvent.

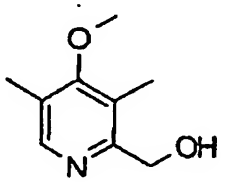
The water content in the solvent system shall preferably be near or above the saturation point of the organic solvent used. By this, a higher amount of pyrmethyl alcohol (Ia) is allowed to react and form the pyrmethyl chloride (Ib). The amount of water may be added before, during or after the charging of the chloro-dehydroxylating agent, such as thionyl chloride. An optimum range of water present during Step 1 is between 0.3 and 5.5 mg water/ml of water immiscible organic solvent, preferably between 0.3 and 5.0 mg water/ml, or between 0.4 and 2.4 mg/ml, and most preferably between 1.0 and 2.4 mg/ml. If the water content is lower than the saturation point of the organic solvent used i.e. for toluene, less than 0.3 mg/ml, the reaction is slow and it has a tendency to stop before full conversion has been achieved. In average, a conversion of 25-50 % is obtained when toluene, having a water content of less than 0.1 mg/ml, is used as the solvent system. Such a reaction leads to a high content of pyrmethyl alcohol (Ia) in the reaction mixture after Step 1. It is inconvenient to have a high content of pyrmethyl alcohol present in the crude product of pyrmetazole (I) after Step 2. We have found that if about 1 %, or more, of pyrmethyl alcohol (Ia) is left in the reaction mixture, this component has an adverse effect

on both the turnover and the enantioselectivity achieved in the asymmetric oxidation of pyrmetazole into esomeprazole.

The present invention is an improvement of the first two steps in the process described in WO 97/22603. The reaction sequence, from pyrmethyl alcohol (Ia) via pyrmethyl chloride (Ib) to pyrmetazole (I), is carried out in one common solvent system, comprising a water immiscible organic solvent and a specified amount of water, which is used throughout the reaction sequence. The new improved process for the manufacture of 5-methoxy-2(((4-mehoxy-3,5-dimethyl-2-pyridinyl)-methyl)-thio)-1H-benzimidazole (pyrmetazole) can in more detail be described by Step 1 and Step 2 below, both performed in a water immiscible organic solvent and with a specified amount of water added:

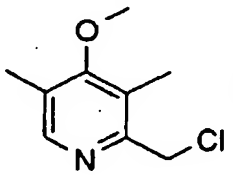
Step 1: Chloro-dehydroxylation:

Reacting (4-methoxy-3,5-dimethyl-2-pyridinyl)methyl alcohol (pyrmethyl alcohol) of the formula Ia



Ia

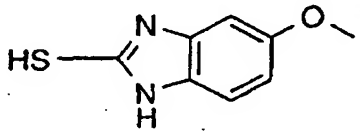
with a chloro-dehydroxylating agent, such as thionyl chloride, providing (4-methoxy-3,5-dimethyl-2-pyridinyl)methyl chloride (pyrmethyl chloride) of the formula Ib



x HCl Ib;

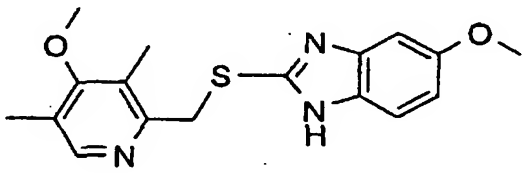
Step 2: Coupling reaction:

Reacting (4-methoxy-3,5-dimethyl-2-pyridinyl)methyl chloride of the formula Ib, prepared in Step 1 above, with 2-mercapto-5-methoxybenzimidazole (metmercazole) of the formula Ic



Ic

in the presence of a base such as, sodium hydroxide or potassium hydroxide, providing 5-methoxy-2(((4-methoxy 3,5-dimethyl-2-pyridinyl)methyl)thio)-1H-benzimidazole (pyrmetazole) of the formula I



I

The pyrmetazole is then further processed to the final products, omeprazole or esomeprazole.

The present invention provides an improvement associated to Step 1 in the manufacturing of pyrmetazole, by a more complete conversion and reproducible yield of pyrmethyl alcohol (Ia) and pyrmethyl chloride (Ib) respectively. The advantageous effect of water present during the chloro-dehydroxylation reaction, Step 1, is surprisingly as this type of chloro-dehydroxylating agents are regarded as incompatible with water, i.e. thionyl chloride reacts violently with water and excess of thionyl chloride is usually hydrolysed after a reaction by an addition of water.

More specifically, the aim with the present invention has been to improve Step 1, the chloro-dehydroxylation step, in the process for preparation of pyrmetazole (I) used in the synthesis of omeprazole or esomeprazole, i.e. to obtain a more efficient conversion of the pyrmethyl alcohol (Ia), a reaction step that is common for both the synthesis of esomeprazole and omeprazole. It has, surprisingly, been shown that presence of a specified amount of water reduces the amount of remaining pyrmethyl alcohol (Ia) i.e. the conversion of pyrmethyl alcohol (Ia) according to Step 1 is more complete. A small amount of water present in the reaction mixture lead to a better conversion, and a more efficient use of pyrmethyl alcohol (Ia) and a product of high yield and high purity.

According to the process described in WO 97/22603 the crude product, pyrmetazole (I), from Step 2 is further processed to omeprazole in a consequtive reaction sequence. There is no isolation or purification performed during the reaction sequence, which is preferable with respect to process simplicity and economy. However, residues of pyrmethyl alcohol (Ia) from Step 1 have been found in the product mixture of pyrmetazole (I) in Step 2.

It has been found that traces of pyrmethyl alcohol (Ia) have disadvantageous effects upon the oxidation of pyrmetazole (I) to omeprazole and especially then in the asymmetric oxidation of pyrmetazole (I) to esomeprazole. Such traces of pyrmethyl alcohol (Ia) results in reduced turnover and enantio-selectivity in the asymmetric oxidation and give a product with less purity and in lower yield. Thus, the obtained enantiomeric excess of esomeprazole is depending on a high purity of the intermediate compound pyrmetazole (I). The impact of levels from about 1% or above of pyrmethyl alcohol has been investigated.

The presence of water in the chloro-dehydroxylation reaction, Step 1, is of outmost importance to obtain pyrmethyl chloride (Ib) and thereby pyrmetazole (I) in high yield and with a high purity without any requirements of isolation or purification. The required amount of water may be charged from the beginning, or being added during or after the addition of a suitable chloro-dehydroxylating agent, such as thionyl chloride. Preferably a small specified amount of water is charged at the beginning of the reaction. The addition of

water during the process may also be used as a way to re-start an incomplete reaction to improve the yield and product purity. The present invention provides a more efficient use of the chloro-dehydroxylating agent.

Furthermore, the presence of water in Step 1 provides a safer, and more robust process, as it also reduces the different risks connected with this type of reactions, i.e. such as accumulation of thionyl chloride or reactive reaction intermediates. Thus, avoiding the risk of a late rapid exothermic reaction to occur. However, there exists other options to get complete and /or high conversion of pyrmethyl alcohol (Ia) in Step 1, and to avoid, or minimise, traces of pyrmethyl alcohol (Ia) in Step 2, These options can be, for instance, an extended reaction time, raised reaction temperature or increased excess of thionyl chloride. However, these options are not favored in view of an effective production of the final products, omeprazole and esomeprazole.

The examples that follow will further illustrate the improved process of the invention. These examples are not intended to limit the scope of the invention as defined hereinabove or as claimed below.

EXAMPLES

Example 1

Pyrmethyl alcohol, 8.82 g (52.7 mmol), was dissolved in toluene, saturated with water, 74 ml (water content 0.4 mg/ml according to Karl Fisher titration). To the stirred solution, at 10°C, thionyl chloride, 8.15 g (68.5 mmol), was added slowly over 60 minutes (flow rate 0.083 ml/min). A white precipitate was formed. The conversion of pyrmethyl alcohol into pyrmethyl chloride was followed by HPLC, (column: Nova-Pak C 18, 4 µm, 3.9*150 mm). A fast reaction was recorded, reaching 99 % conversion after completed addition of thionyl chloride.

Example 2

Pyrmethyl alcohol, 8.81 g (52.6 mmol), was dissolved in a mixture of toluene, 75 ml (water content 0.04 mg/ml according to Karl Fisher titration) and water, 180 µl (10 mmol, equivalent to about 2.4 mg /ml of water in toluene). To the stirred solution, at 10°C, thionyl chloride, 8.15 g (68.5 mmol), was added slowly over 60 minutes (flow rate 0.083 ml/min). A white precipitate was formed. The conversion of pyrmethyl alcohol into pyrmethyl chloride was followed by HPLC as in Example 1. A fast reaction was recorded, reaching 99 % conversion after completed addition of thionyl chloride. The reaction temperature was adjusted to 20°C and methanol, 40 ml, was added to stop the reaction. A solution of the crude product, pyrmethyl chloride was obtained, with a purity of 99.6 % (HPLC), and with a pyrmethyl alcohol residue of 0.3 %.

Example 3

Pyrmethyl alcohol, 8.82 g (52.7 mmol), was dissolved in toluene, 75 ml (water content 0.04 mg/ml according to Karl Fisher titration). To the stirred solution, at 10°C, thionyl chloride, 8.15 g (68.5 mmol), was added slowly over 60 minutes (flow rate 0.083 ml/min). A white precipitate was formed immediately. The obtained reaction mixture was stirred and the reaction followed by HPLC, as in Example 1, for an additional 3.5 hours (conversion declined and stopped at about 30%). Water, 180 µl (10 mmol), was added, to re-start the reaction, yielding a high conversion (> 90%) within 30 minutes after the addition.

Example 4

Pyrmethyl alcohol (8.8 g, 52.6 mmol) was dissolved in toluene (75 ml, water content 0.12 mg/ml) moistened with water (180 µl, 10 mmol) at room temperature. To the stirred solution, at 25-30 °C, thionyl chloride (8.15 g, 68.5 mmole) was added slowly over 60 min.

(flow rate of 0.083 ml/min). Conversion of the reaction was analysed with HPLC as in Example 1. Conversion over 99.5%. Water (2.3 ml) was added to quench any excess of thionyl chloride.

An alkaline (13.5 g, 168.3 mmol 50 % w/w sodium hydroxide) aqueous (80 ml) solution of metmercazole (9.8 g, 54.2 mmol) was added followed by additional sodium hydroxide (8.8 g, 110.5 mmol, 50 % w/w sodium hydroxide) to reach pH>12.5. The temperature was allowed to increase to 45 °C during the additions. The reaction mixture was left with vigorous stirring for approximately two hours at 45 °C. The agitating was interrupted and the phases were left to separate. The aqueous phase was discarded. The organic phase, comprising pyrmetazole, was washed with water and was analysed for residues of pyrmethyl alcohol (less than 0.1 %mol).

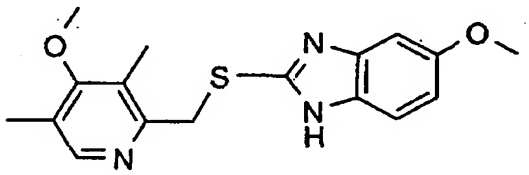
Example 5

Pyrmethyl alcohol (8.8 g, 52.6 mmol) was dissolved in toluene (75 ml, water content 0.12 mg/ml) moistened with water (375 µl, 20.8 mmol) at room temperature. To the stirred solution , at 25-35 °C, thionyl chloride (9.33 g, 78.4 mmol) was added slowly over 60 min. (flow rate of 0.095 ml/min). Conversion of the reaction was analysed with HPLC as in Example 1. Conversion over 99.5 %.

The synthesis continued in the same way as described in Example 4. The product phase, comprising pyrmetazole, was analysed for residue of pyrmethyl alcohol (less than 0.1 %mol).

CLAIMS.

1. A process for the manufacture of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]-thio]-1H-benzimidazole of formula I

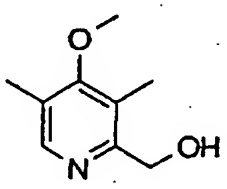


I

from (4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl alcohol comprising the following reaction steps carried out in a consecutive order in one main solvent system without isolation of the intermediates formed during the process

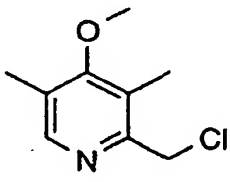
Step 1:

reacting (4-methoxy-3,5-dimethyl-2-pyridinyl)methyl alcohol (pyrmethyl alcohol) of the formula Ia



Ia

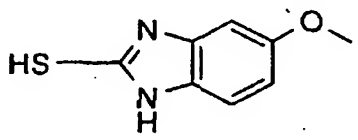
with a chloro-dehydroxylating agent, providing (4-methoxy-3,5-dimethyl-2-pyridinyl)methyl chloride (pyrmethyl chloride) of the formula Ib



x HCl Ib;

Step 2:

reacting (4-methoxy-3,5-dimethyl-2-pyridinyl)methyl chloride of the formula Ib, prepared in Step 1 above, *with 2-mercapto-5-methoxybenzimidazole* (metmercazole) of the formula Ic



Ic

in the presence of a base, providing 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (pyrmetazole) of the formula I

c h a r a c t e r i z e d in that the solvent system, common for the whole reaction sequence, comprises water immiscible organic solvent with a specified amount of between 0.3 and 5.5 mg water / ml water immiscible organic solvent added.

2. A process according to claim 1 wherein the water immiscible organic solvent is toluene.

3. A process according to claim 1 wherein the water immiscible organic solvent is ethyl acetate.

4. A process according to claim 1, characterized in that the specified amount of water is present from the start of the reaction according to Step 1.

5. A process according to any one of claims 1 and 4, characterized in that the specified amount of water is added during the charging of the chloro-dehydroxylating agent in the reaction according to Step 1.

6. A process according to any one of claims 1 to 5, characterized in that the specified amount of water is added after charging of the chloro-dehydroxylating agent in the reaction according to Step 1.

7. A process according to claim 1, characterized in that the specified amount of water is 0.3 – 5.0 mg/ml of water immiscible organic solvent.

8. A process according to claim 1, characterized in that the specified amount of water is 0.4 – 2.4 mg/ml of water immiscible organic solvent.

9. A process according to claim 1, characterized in that the specified amount of water is 1.0 – 2.4 mg/ml of water immiscible organic solvent.

10. A process according to any one of claims 1 to 9, characterized in that the reaction according to Step 1 is carried out at a temperature between -5°C and +45°C.

11. A process according to any one of claims 1 to 9, characterized in that the temperature is between -5°C and +35°C.

12. A process according to any one of claims 1 to 9, characterized in that the temperature is between +10°C and +35°C.

13. A process according to any one of claims 1 to 9, characterized in that the temperature is between +25°C and +35°C.

14. A process according to any one of claims 1 to 13, characterized in that the chloro-dehydroxylating agent is thionyl chloride.

15. 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (pyrmetazole) prepared according to any of the claims 1 to 14.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/001602

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/12
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM. ABS DATA, EPO-INTERNAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9722603 A1 (ASTRA AKTIEBOLAG), 26 June 1997 (26.06.1997)	14
A	--	1-13

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance
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"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 January 2004	22-01-2004
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Nebil Gecer/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT
Information on patent family members

01/12/2003

International application No.
PCT/SE 2003/001602

WO	9722603	A1	26/06/1997	AT	205201	T	15/09/2001
				AU	704422	B	22/04/1999
				AU	1155097	A	14/07/1997
				CA	2238864	A	26/06/1997
				CN	1113879	B	09/07/2003
				CN	1204332	A	06/01/1999
				CZ	288661	B	15/08/2001
				CZ	9801685	A	16/09/1998
				DE	868423	T	02/06/1999
				DE	69615052	D,T	27/06/2002
				DK	868423	T	03/12/2001
				EE	3768	B	17/06/2002
				EE	9800183	A	15/12/1998
				EP	0868423	A,B	07/10/1998
				SE	0868423	T3	
				ES	2125210	T	01/03/1999
				HK	1010539	A	00/00/0000
				HR	960581	A,B	28/02/1998
				HU	9900110	A	28/03/2000
				IL	124856	A	01/12/2002
				JP	2000502101	T	22/02/2000
				NO	314306	B	03/03/2003
				NO	982624	A	08/06/1998
				NZ	324482	A	28/04/2000
				PL	327334	A	07/12/1998
				PT	868423	T	28/02/2002
				RU	2166502	C	10/05/2001
				SE	521100	C	30/09/2003
				SE	9504503	A	16/06/1997
				SI	868423	T	00/00/0000
				SK	76898	A	02/12/1998
				SK	282347	B	07/01/2002
				TR	9801070	T	00/00/0000
				TW	460474	B	00/00/0000
				US	5958955	A	28/09/1999
				ZA	9610067	A	17/06/1997